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Neuronal Activity in the Primate Motor Thalamus During Visually Triggered and Internally Generated Limb Movements

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van Donkelaar, P., J. F. Stein, R. E. Passingham, and R. C. Miall. Neuronal activity in the primate motor thalamus during visually triggered and internally generated limb movements. *J. Neurophysiol.* 82: 934–945, 1999. Single-unit recordings were made from the basal-ganglia- and cerebellar-receiving areas of the thalamus in two monkeys trained to make arm movements that were either visually triggered (VT) or internally generated (IG). A total of 203 neurons displaying movement-related changes in activity were examined in detail. Most of these cells (69%) showed an increase in firing rate in relation to the onset of movement and could be categorized according to whether they fired in the VT task exclusively, in the IG task exclusively, or in both tasks. The proportion of cells in each category was found to vary between each of the cerebellar-receiving [oral portion of the ventral posterolateral nucleus (VPLo) and area X] and basal-ganglia-receiving [oral portion of the ventral lateral nucleus (VLo) and parvocellular portion of the ventral anterior nucleus (VApc)] nuclei that were examined. In particular, in area X the largest group of cells (52%) showed an increase in activity during the VT task only, whereas in VApc the largest group of cells (53%) fired in the IG task only. In contrast to this, relatively high degree of task specificity, in both VPLo and VLo the largest group of cells (~55%) burst in relation to both tasks. Of the cells that were active in both tasks, a higher proportion were preferentially active in the VT task in VPLo and area X, and the IG task in VLo and VApc. In addition, cells in all four nuclei became active earlier relative to movement onset in the IG task compared with the VT task. These results demonstrate that functional distinctions do exist in the cerebellar- and basal-ganglia-receiving portions of the primate motor thalamus in relation to the types of cues used to initiate and control movement. These distinctions are most clear in area X and VApc, and are much less apparent in VPLo and VLo.

INTRODUCTION

The cerebellum and basal ganglia project via the thalamus to widespread yet overlapping parts of the cortex including areas involved with the control of movement. At the level of the thalamus, the projections from the deep nuclei of the cerebellum and the internal segment of the globus pallidus (GPi) remain largely segregated (Roullier et al. 1994; Sakai et al. 1996). This level of neuroanatomic segregation, although not as complete at the level of the cortex as was once believed, has led to the suggestion that the cerebellum and basal ganglia and their ascending projections also may be differentiated on a functional basis. The exact nature of this functional differentiation has been the focus of numerous studies. For example,

the cerebellum has been shown to be preferentially involved in movements that are initiated and/or guided by the presence of sensory cues (Jueptner et al. 1996; Mushiaki and Strick 1993; Stein and Glickstein 1992; van Donkelaar and Lee 1994). In contrast, the basal ganglia have been shown to be preferentially involved in movement selection (Jueptner et al. 1997), the inhibition of undesired movements (Mink 1996), the sequencing of a series of movements (Boecker et al. 1998; Brotchie et al. 1991; Kermadi and Joseph 1995), and the production of memorized or internally generated movements (Crawford et al. 1989; Hikosaka and Wurtz 1985; Mushiaki and Strick 1995). These functions attributed to the basal ganglia are not necessarily mutually exclusive. In fact, a feature that may be common to each is the selection of responses based on internal cues. Thus it has been suggested that at a very general level the cerebellum may be involved preferentially in triggering and guiding movements based on external sensory stimuli, whereas the basal ganglia may be involved preferentially in selecting movements based on internal cues. Having said this, it is important to emphasize that this dissociation is not complete. In other words, the cerebellum also appears to be involved to a certain extent in movements based on internal cues and the basal ganglia in movements triggered and guided by external stimuli (Passingham 1993; Stein 1986). Indeed, there is evidence to suggest that the functional specificity described above may be restricted to certain portions of the cerebellar- and basal ganglio-thalamo-cortical systems (see following text). Thus the important point is that different anatomically segregated subcircuits arising from the basal ganglia and cerebellum appear to be involved to varying degrees in the performance of movements based on external versus internal cues.

The purpose of the present experiment was to examine the extent of this functional specificity at the level of the thalamus. Previous thalamic recording studies have shown clear limb-movement-related activity in both cerebellar- and basal-ganglia-receiving nuclei (e.g., Anderson and Turner 1991; Butler et al. 1992, 1996; Forlano et al. 1993). In the present study, we recorded from cells in different portions of the primate motor thalamus during movements that were either visually triggered or internally generated. We looked in particular at activity in the cerebellar-receiving nuclei VPLo (oral portion of the ventral posterolateral nucleus) and area X and the basal-ganglia-receiving nuclei VLo (oral portion of the ventral lateral nucleus) and VApc (parvocellular portion of the ventral anterior nucleus). We predicted that the degree of functional specificity observed for each of these nuclei would be dependent on its

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pattern of connectivity within each subcortico-thalamo-cortical pathway.

Some insight into this issue can be gained by examining how output cells in the cerebellum and basal ganglia that project to specific portions of the motor thalamus respond in different movement contexts. For example, Mushiake and Strick (1993) have demonstrated that the majority of cells in the caudal portion of the cerebellar dentate nucleus display a preference for movements based on visual cues—firing to a greater extent when a visual target triggers and guides the response compared with when the same movements are generated from memory. This area of the dentate projects mainly to area X (Strick et al. 1993), implying that cells in area X also may display a preference for visually triggered and guided movements. By contrast, Mushiake and Strick (1993) also found that cells in the more rostral portion of the dentate did not differentiate as clearly between visually guided and memory-guided arm movements. The rostral dentate projects mainly to VPLo (Strick et al. 1993), implying that cells in this part of the thalamus may not differentiate between these two modes of movement as clearly as cells in area X.

Studies that have examined these functional distinctions in basal ganglia output cells have produced less consistent results. Mink and Thach (1991b) and Inase et al. (1996a) found that inactivation of the GPi caused similar deficits in both visually triggered and memory-guided or self-paced movements: namely, a flexor drift in the affected arm. This led these researchers to conclude justly that the basal ganglia was involved in turning off or biasing muscle activity to allow a particular movement to occur regardless of the context. Consistent with their infusion results, Mink and Thach (1991a) found that the activity of cells in the GPi did not differentiate between several different modes of movement including visually triggered and self-paced movements. A similar lack of task specificity has been found in cells located in the putamen (Kimura et al. 1992) and the SNpr (Hikosaka and Wurtz 1983a,b). By contrast, Brotchie and coworkers (1991) suggested from the results of their experiments that activity in GPi cells provided an internal cue that contributed to the switching from one movement to another within a predictable sequence. Importantly, the magnitude of this activity dropped off considerably when the sequence became unpredictable (and therefore driven by external sensory cues).

How can these differing results be accounted for while still maintaining that the basal ganglia may be involved in some way in movement selection based on internal cues? One possible explanation is with respect to the location within the GPi in particular at which the inactivation or recording took place. Mink and Thach (1991b) and Inase and coworkers (1996a) inactivated the mid- to ventral half of GPi and Mink and Thach (1991a) recorded from the same area. Kimura and coworkers (1991) recorded from the putamen which projects to the ventral two-thirds of the globus pallidus (Smith and Parent 1986). On the other hand, Brotchie and colleagues (1991) sampled “from the full extent of the GP” (p.1671). Thus it may be that some portions of the GPi contribute preferentially to internally cued actions and that the mid- to ventral half of the GPi is not one of those areas. Mushiake and Strick (1995) explicitly tested this possibility and found that a large proportion of cells (65%) located in the dorsal part of the GPi fired preferentially during memory-guided arm movements, whereas cells located more

ventrally did not differentiate between visually guided and memory-guided arm movements.

How such functional neuroanatomic distinctions may be reflected in the basal-ganglia-receiving portions of the thalamus is not clear. Cells located more dorsally in the GPi project mainly to lateral and rostral aspects of VLo and VApc. In contrast, cells located more ventrally in the GPi project to the middle portion of VLo (DeVito and Anderson 1982). These results and those of Mushiake and Strick (1995) imply that cells within VApc may be more likely to display a preference for internally driven movements than cells within VLo, although it is not clear how much of a difference there would be because of the overlap in the pallidothalamic projections.

To provide further insight into these questions, we describe experiments in which single-unit recordings were made in the cerebellar- and basal-ganglia-receiving portions of the primate motor thalamus during visually triggered and internally generated limb movements. A preliminary report of portions of the present data were presented previously (van Donkelaar et al. 1997a).

METHODS

Animals and apparatus

Two juvenile rhesus macaque monkeys (*Macaca mulatta*), weighing between 4.8 and 5.2 kg, served as subjects in the present experiment. All procedures for animal care and use were in accord with the “Guiding Principles in the Care and Use of Animals” (American Physiological Society 1991). Each monkey was trained to perform reaching movements with the right hand using a manipulandum that allowed multijoint responses in a two-dimensional workspace. The manipulandum was positioned underneath an angled semisilvered mirror onto which could be projected the virtual image of a target (1 cm²) from an overhead computer screen. The manipulandum was made visible through the mirror with diffuse illumination of the homogeneous background. The position of the manipulandum was measured in the anterior-posterior and medial-lateral dimensions with two precision potentiometers. The monkey was rewarded for making forward movements with the manipulandum starting just in front of its torso and ending ~15 cm away with the arm almost fully extended.

Behavioral tasks

Two behavioral tasks were used. In both, the monkey was required to wait before initiating a response with his hand grasping the manipulandum at the start position located ~5 cm directly in front and at the midline of his torso. In the visually triggered task (VT), the target then would appear after a variable length of time (2–3 s), and the monkey was rewarded for accurately reaching it with the manipulandum. In 80% of the trials, the target would appear at the center of the screen directly in front of the monkey. In the remaining 20% of trials, the target would appear 5 cm to the left or right of center. These trials were included to keep the monkey from producing stereotyped movements to the central target. In the internally generated task (IG), no target appeared, and the monkey was rewarded simply for making a spontaneous movement of the same extent (i.e., 15 cm) as in the VT task. A minimum interval of 3 s between each movement was required, and early movements were signaled by a warning tone after which the monkey was required to return to the starting position. Thus in VT trials the target provided a visual cue about when and where to reach, whereas in IG trials, no such cue was present. In both tasks, the monkey was allowed to return to the start position on successful completion of the response (i.e., no “target hold time” was required). The two tasks were presented in separate blocks of trials each lasting

~2–5 min, depending on how long it took the monkey to complete ≥ 20 successful trials.

Surgical procedures

When each monkey was trained sufficiently on both tasks, it was anaesthetized [ketamine hydrochloride (10 mg/kg im) and alphaxalone/alphadolone acetate (5 mg/kg iv)], and a vertically oriented recording chamber was implanted stereotaxically over the left thalamus under aseptic conditions. In addition, two small stainless steel tubes were horizontally positioned in front of and behind the chamber and cemented to the skull using dental acrylic. These subsequently were used to stabilize the head during recording sessions. During the surgery, frontal and sagittal ventriculographs were obtained to aid in the determination of the location of the thalamus with respect to the recording chamber. Analgesics and antibiotics were given postoperatively as required.

Neuronal recording procedures

The activity of isolated single units was recorded with glass-insulated tungsten microelectrodes (impedance 1–2 M Ω) inserted through a stainless steel guide tube extended to within ~5 mm of the dorsal surface of the thalamus. Isolated waveforms were passed through a time-voltage template (CED Spike2) to discriminate and produce a pulse for each spike with a temporal resolution of 0.1 ms. The potential relation between neuronal activity and the experimental task initially was assessed by inducing the monkey to reach toward food rewards presented by the experimenter. If the cell activity was modulated in this task, then further tests were completed to ensure that it was due more specifically to arm movement and not to associated postural adjustments of the axial musculature or the legs or to facial movements associated with licking/chewing. Briefly, these tests consisted of examining the cell's response to passive rotation of the relevant joints and active movements of the lower limbs and face (in response to unexpected touches or directly administered food rewards, respectively). If the cell responded exclusively to lower limb or face movement or appeared to be related to the postural component of the reaching response, it was not tested in the experimental task. If on the other hand the cell displayed arm-movement-related activity, its response to the two different tasks was examined in detail. Although we did not systematically examine cells with presumed leg-, torso-, and face-related activity, we did note that there was some somatotopy present especially in VPLo and, to a lesser extent in VLo. In particular, as we moved mediolaterally with our penetrations, we tended to encounter face, then arm, then leg cells. This is consistent with previous reports that have examined motor thalamic somatotopy in more detail (Vitek et al. 1994, 1996). Finally, we also qualitatively tested the response of cells to saccadic and smooth pursuit eye movements by inducing the monkey to look at or visually track food rewards beyond their reach. We encountered several cells that appeared to have eye-movement-related activity and were likely located in VAmc (magnocellular portion of the ventral anterior nucleus). Such cells were not investigated further.

For the arm-movement-related cells, spike frequency histograms triggered on movement onset (determined using a velocity threshold) were constructed on-line to allow the experimenter to visually determine whether the isolated cell was modulated significantly by either of the experimental tasks. In addition, histograms triggered on target onset also were generated for the VT task. These were used to confirm that the activity was movement-related rather than a long-latency sensory response to the visual stimulus. In all cases, the changes in activity were brisker and of a greater magnitude when triggered on movement onset rather than target onset. The spike trains, perimovement time histograms, timing of target appearance (in the VT task) and reward delivery, and the movement trajectory all were saved to computer for subsequent quantitative analysis.

Data analysis

Perimovement time histograms were constructed for a 3-s period starting 1.5 s before the onset of movement and ending 1.5 s after the onset of movement (40-ms bins). The mean and SD for the baseline activity was calculated for the 500-ms period from 1.5 to 1 s before movement onset. Movement-related changes in neuronal firing rate were considered significant when the mean firing rate increased or decreased by ≥ 2 SD from the baseline activity for at least three consecutive bins. The onset time of neuronal activity (the 1st of these significant bins) was measured relative to the beginning of movement. The depth of modulation also was calculated as the average percentage change during the movement relative to the baseline firing rate. It is possible that preparatory activity in the IG task may start well before our baseline period (see e.g., Schultz and Romo 1992), thereby biasing the analysis of movement-related changes. We tested for this by comparing the magnitude of the baseline activity in the VT and IG tasks for the population of cells in each of the thalamic nuclei examined. In every case no significant differences were found (*t*-test, $P > 0.05$), confirming that the preparatory activity was confined to the period just before the onset of movement.

Thalamic stimulation

In separate sessions, we used thalamic stimulation as an aid to help us determine whether our recording sites were in cerebellar- or basal-ganglia-receiving areas of the thalamus. Several recent microstimulation experiments have demonstrated that movement can be elicited at low thresholds from VPLo and VLc (caudal portion of the ventral lateral nucleus) but not any other thalamic nuclei (Buford et al. 1996; Miall et al. 1998; Vitek et al. 1996). Brief (100–300 ms) trains of biphasic stimulation (negative/positive, 0.2 ms per phase, 0.3-ms interpulse interval) were applied at a rate of 200 Hz at selected sites along the presumed borders between the cerebellar- and basal-ganglia receiving areas. Motor responses were monitored by visual observation and palpation of the arm and hand. Stimulus current started at 10 μ A and was raised incrementally to a maximum of 150 μ A. When movements were elicited by the stimulation, a threshold was determined by reducing current until a consistent (3 trials in a row) but barely detectable muscle contraction was observed visually or by palpation. In addition, in the final sessions, small electrolytic marking lesions were made along selected tracks by passing DC current (20 μ A, 30 s) through a microelectrode.

Histological procedures and identification of thalamic nuclei

At the end of the experiments each monkey was killed with a lethal dose of pentobarbital sodium. They subsequently were perfused transcardially with saline, followed by 10% buffered Formalin. The brain was removed from the cranium and fixed, frozen, and sectioned in the sagittal plane at 50 μ m. Every fifth section was stained with cresyl violet and mounted.

The thalamus was parcellated according to the nomenclature and cytoarchitectonic criteria of Olszewski (1952) and Matelli and colleagues (1989). Briefly, VPLo is located in the ventrolateral part of the ventrolateral thalamus and is separated anteriorly from VLc by VLo. VPLo possesses a heterogeneous cellular population characterized by uniformly distributed large, densely stained multipolar cells intermingled with cells of small diameter. Area X is located medial to VPLo and VLo. It is composed of lightly stained uniformly distributed large fusiform cells intermingled with small groups of lightly stained large multipolar cells. VLo is located lateral to area X posteriorly and VApc more anteriorly. It is characterized by darkly stained small round or oval cells densely packed in clusters separated by poorly populated areas. Finally, VApc is situated at the most rostral extent of the ventrolateral thalamus. It borders on VAmc medially and the VLo

laterally. It is composed of medium-sized lightly stained irregularly distributed cells.

Nuclear borders and electrolytic marking lesions were identified for each histological section. The nuclear borders were identified based on the characteristic nuclear cell densities and sizes described in the preceding text. Recording and stimulating positions were reconstructed based on their microdrive coordinates and, where possible, gliosis associated with the electrode tracks, relative to the marker lesions. Several additional pieces of evidence were used to help confirm the reconstructions. First, lateral and coronal X-rays taken after each experiment with the electrode in place were compared with the ventriculographs obtained during surgery to confirm the medio-lateral and anteroposterior position of the electrode with respect to the motor thalamus. Second, the high-frequency discharge characteristic of the reticular nucleus and the somatosensory responses characteristic of the caudal portion of the ventral posterolateral nucleus (VPLc) aided in the definition of the dorsoventral and posteriolateral borders, respectively, of the motor thalamus. Third, the results from the microstimulation sessions were used to confirm the location of VPLo/VLc; previous studies have demonstrated that the threshold for electrical stimulation of movement rises dramatically as one moves rostrally from VPLo/VLc to VLo and VApc (Buford et al. 1996; Miall et al. 1998; Vitek et al. 1996). The reconstructed recording positions were mapped onto specific thalamic nuclei based on the cytoarchitectonic criteria described in the preceding text. These maps then were used to obtain cell counts and task specific frequencies in each of the nuclei examined. However, because of the difficulty in determining nuclear borders in the thalamus, any cells estimated to be on or near the borders were eliminated from subsequent analysis. Of the 224 cells from which recordings originally were made, 21 were discarded for this reason. Included in this group were several cells ($n = 3$) that fell near the border between VPLo and VLc. Other than these cells we did not record any others within VLc.

RESULTS

Movement characteristics

It was important to confirm that the VT and IG movements had similar temporal and kinematic characteristics. This would allow us to exclude the possibility that differences in neuronal activity between the two tasks were due simply to the fact that the movements themselves were different. Figure 1, *A* and *B*, provides the average peak velocity and movement time in the VT and IG tasks for each monkey. A 2×2 (task type \times monkey) repeated-measures ANOVA (RM ANOVA) performed on each of these dependent variables revealed no significant effects. Thus movement time and peak velocity were similar for both tasks and for both monkeys.

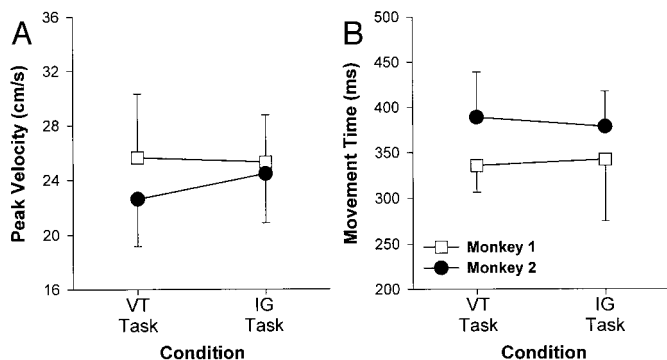


FIG. 1. Mean peak velocity (*A*) and movement time (*B*) for monkey 1 (□) and monkey 2 (●) across all trials in the visually triggered (VT) and internally generated (IG) tasks. Error bars, 1 SD.

General patterns of neuronal activity

We recorded from a total of 203 cells (110 in *monkey 1* and 93 in *monkey 2*) that displayed changes in activity in relation to at least one of the tasks. These cells fell into three general categories related to the nature and timing of their firing pattern. Examples of each of these categories are provided in Fig. 2. The first group of cells showed a significant increase in firing rate before and/or during the movement (Fig. 2*B*). The second group displayed a significant decrease in firing rate at this time (Fig. 2*C*). The third group showed an increase in firing rate exclusively at the end of the movement (Fig. 2*D*). These late onset cells could be coding the antagonist braking of the outward movement, the agonist activity of the return movement, or the delivery of the reward. This issue will be addressed in a subsequent publication. We never encountered cells that displayed a combination of these activity categories across task types (e.g., an increase in firing rate during the VT task and a decrease in firing rate during the IG task).

Across the 203 cells examined, the majority displayed an increase in firing rate before and/or during the movement (69%), with lower percentages showing decreases around the movement (22%) or increases exclusively at the end of the movement (9%). Moreover, as can be seen in Fig. 3, *A–D*, the percentage distributions of these three categories of cells appeared to be similar in each of the four main thalamic nuclei (VPLo, area X, VLo, VApc, respectively) from which we recorded. χ^2 analysis revealed a significant effect of activity category across the four nuclei ($\chi^2 = 11.53$, $df = 2$, $P < 0.0003$). Analytical comparisons demonstrated that the significant effect of activity category was due to differences in the percentage of cells showing an increase in activity before and/or during the movement versus the percentage of cells in the other two categories. Furthermore the differences between these latter two categories were not significant. Thus in all four nuclei tested the largest percentage of cells increased their activity before and/or during the movement with significantly lower percentages of cells showing decreases around the movement or increases only at the end of movement. Thus the different cerebellar- and basal-ganglia-receiving nuclei could not be differentiated in terms of their general patterns of activity.

Task-specific increases in activity

Because cells displaying an increase in activity around the movement constituted the largest group encountered, we decided to assess the response characteristics of this group in further detail. In particular, we categorized these cells as to whether they fired in both the VT and IG task, exclusively in the VT task, or exclusively in the IG task. To be categorized as “exclusively” related to a particular task type, a cell had to display a significant increase in firing rate for that task and no significant increase above baseline levels in the other task. This is a strict criterion that excludes cells that show a “preference” for one task, that is, cells that fire with a greater magnitude in one task than they do in the other (Mushiake and Strick 1993, 1995; Mushiake et al. 1991). We included such cells in our first category (i.e., cells that fired in both tasks) and have analyzed their response characteristics in relation to each task within each of the nuclei examined (see in the following text).

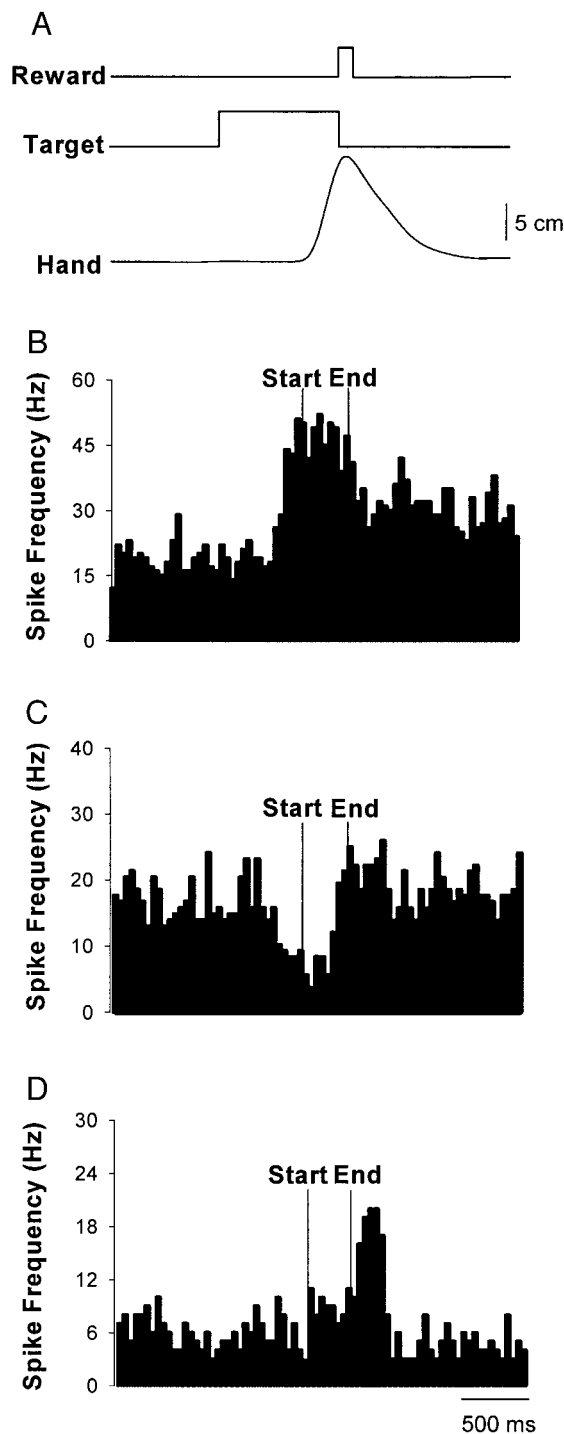


FIG. 2. Examples of 3 different categories of movement-related activity in the motor thalamus. *A*: time course of target appearance, hand movement, and reward delivery in a typical VT trial. *B*: example of a cell from oral portion of the ventral posterolateral nucleus (VPLo) displaying an increase in firing rate before and during the movement. *C*: example of a cell from VPLo displaying a decrease in firing rate before and during the movement. *D*: example of a cell from ventral lateral nucleus (VLo) displaying an increase in firing rate at the end of the movement only. Spike frequency histograms in *B–D* are aligned on movement onset and represent the average firing rates in 40-ms bins across a minimum of 10–15 trials. Start, movement onset; End, finish of movement.

Figure 4 provides examples of each type of response. The cell in Fig. 4A was located in VPLo and displayed significant increases in activity whenever an arm movement was made,

regardless of whether the movement was visually triggered or internally generated. The cell in Fig. 4B was located in area X and fired only when an external target was presented to trigger and guide the movement. When no target was presented and the monkey was required to produce an internally generated response, the cell failed to fire above baseline levels. In contrast, Fig. 4C shows a cell located in VAPc that displayed the opposite characteristics: it fired during internally generated movements, but not during visually triggered responses.

The percentages of cells that fell into each of these categories were calculated for each nucleus. As is clear from Fig. 5, *A–D*, there appeared to be very different percentage distributions for each category within the four nuclei. In VPLo (Fig. 5A) most cells (60%) were active in both tasks, less were active exclusively in the VT task (29%) and relatively few in the IG task only (11%). In area X (Fig. 5B), the largest group of cells were active exclusively in the VT task (52%) with fewer active in both tasks (33%) and only a small number active exclusively in the IG task (15%). In VLo (Fig. 5C), the largest group of cells were active in both tasks (50%), less coded exclusively for the IG task (33%), and relatively few for the VT task only (17%). Finally, in VAPc (Fig. 5D), most cells were active in the IG task only (53%), a smaller number in both tasks (34%), and just a handful in the VT task only (13%). χ^2 analysis revealed a significant two-way interaction between nucleus and activity category ($\chi^2 = 31.53$, $df = 6$, $P < 0.0003$). Analytical comparisons confirmed that the percentages of cells in the largest group within each nucleus were significantly higher than in the remaining two groups. In addition, the percentage differences between these lower two groups were also significant for three of the four nuclei (VPLo, area X, and VAPc). Taken together, these results demonstrate that functional dis-

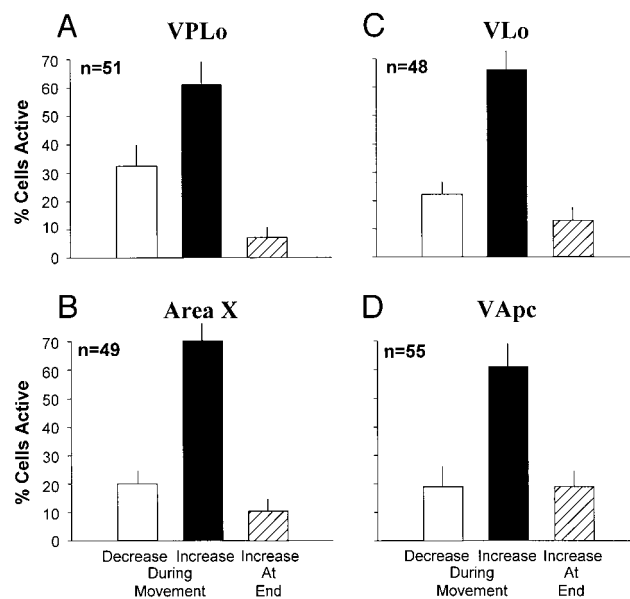


FIG. 3. Percentages of cells displaying the 3 different categories of movement-related activity in each of the 4 main thalamic nuclei examined. Each bar represents the average from the 2 monkeys. □, cells that displayed a decrease in firing rate around the movement; ■, cells that displayed an increase in firing rate around the movement; ▨, cells that displayed an increase in firing rate at the end of the movement only. Number of cells recorded from in each nucleus is shown in each graph (*top left*). Data from VPLo, area X, oral portion of the VLo, and parvocellular portion of the ventral anterior nucleus (VAPc) are shown in *A–D*, respectively. Error bars, 1 SD.

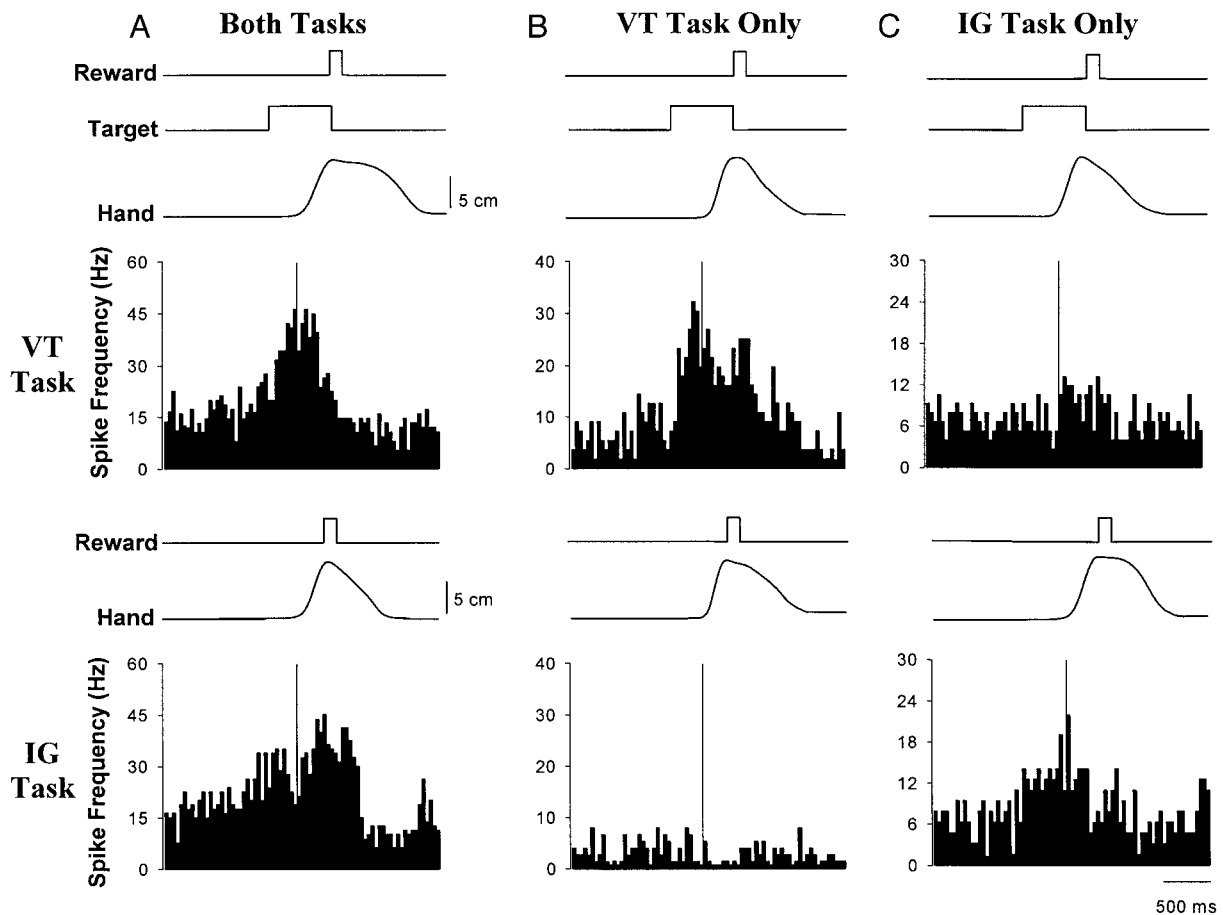


FIG. 4. Examples of cells displaying 3 different types of task-specific increases in movement-related activity. Spike frequency histograms aligned on movement onset (vertical line) are shown for each cell in the VT task (top row) and IG task (bottom row). Time course of target appearance (in the VT task only), arm movement, and reward delivery are shown above each histogram. A: cell located in VPLo that increased its firing rate in both tasks. B: cell from area X that showed an burst of activity in the VT task only. C: cell located in VApc that fired in the IG task but not the VT task.

inctions do exist in certain parts of the cerebellar- and basal-ganglia- receiving portions of the thalamus in relation to the VT and IG tasks. In particular, these distinctions clearly are observed in cells located in area X and VApc. By contrast, most cells in VPLo and VLo do not differentiate between the two types of tasks. Because of the strict criterion in categorizing cells as “exclusive”, we decided to look in more detail at cells that were active in both tasks to see whether they displayed preferences for the VT or IG tasks.

Response characteristics of cells active in both tasks

To assess whether cells that were active in both tasks nevertheless displayed some task-dependent response characteristics, we measured the depth of modulation in each cell and compared these across the two tasks within each nucleus. The depth of modulation was defined as the average percentage change during the movement period relative to the baseline firing rate. On the left side of Fig. 6, A–D, the percentage change in activity in the VT task is plotted against the percentage change in activity in the IG task for each cell that was active in both tasks. Those cells located above the line of unity were preferentially active in the VT task, whereas those falling below the line of unity were preferentially active in the IG task.

On the basis of this simple categorization, there was a trend for more cells to be preferentially active during the VT task in area X (10/13–77%) and VPLo (13/20–65%) and more cells to be preferentially active during the IG task in VApc (9/13–69%) and VLo (9/15–60%). In Fig. 6, A–D, right, the average percentage change in activity is displayed for each task. The means for the individual cells for this variable were submitted to a 4 × 2 (nucleus × task type) RM ANOVA. The results revealed a significant interaction between nucleus and task type [$F(3,122) = 2.76, P < 0.05$]. Post hoc Tukey’s tests showed that this was due to differences in the mean percentage activity change in each task in area X and VApc. On the other hand, the differences between task types in VPLo and VLo were not significant. Thus in addition to possessing many cells that were related exclusively to either the VT or IG task, respectively, area X and VApc also contained a large number of cells that were preferentially active in the VT or IG conditions, respectively. By contrast, although there was a tendency for a greater number of cells in VPLo and VLo to be preferentially excited in the VT and IG tasks, respectively, as a population the activity in these cells did not differentiate between the two conditions.

To determine if the cells became active at different times relative to the beginning of the movement in each task, we also

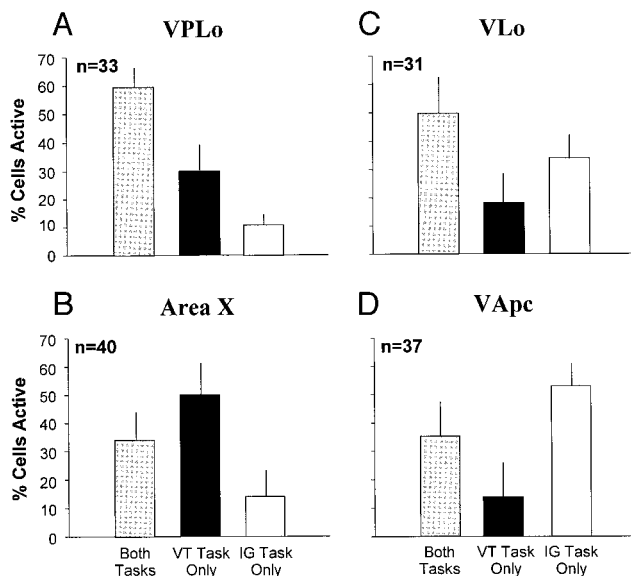


FIG. 5. Percentages of cells within each thalamic nucleus displaying the 3 different types of movement-related increases in activity. Each bar represents the average from the 2 monkeys. □, cells that displayed an increase in firing rate in both the VT and IG tasks; ■, cells that displayed an increase in firing rate in the VT task only; ▤, cells that displayed an increase in firing rate in the IG task only. Number of cells recorded from in each nucleus is shown in each graph (top left). Data from VPLo, area X, VLo, and VApc are shown in A–D, respectively. Error bars, 1 SD.

measured the onset time. This was defined as the time interval between the significant increase in neuronal activity and the beginning of movement. Figure 7, A–D, displays the mean onset times in the VT and IG tasks for the population of cells in each of the thalamic nuclei examined. The means for the individual cells were submitted to a 4×2 (nucleus \times task type) RM ANOVA. The results revealed a significant effect of task type only [$F(1,122) = 8.91, P < 0.05$]. Thus neuronal activity was initiated sooner before the onset of movement in the IG task than in the VT task as has been shown previously for cells in the striatum and SMA (Romo and Schultz 1992; Schultz and Romo 1992). Moreover the lack of a significant interaction between nuclei and task type indicates that the differences in onset times were similar across the four nuclei (see also Anderson and Turner 1991).

Task-specific decreases in activity and late onset cells

We recorded from a total of 44 cells in the two monkeys that displayed decreases in activity at the onset of movement. There were approximately the same number of such cells in the cerebellar- (24/44; 55%) and basal-ganglia-receiving nuclei (20/44; 45%). In terms of the patterns of activity across the two tasks, just over half of the cells (23/44; 52%) decreased their activity in both the VT and IG conditions. A second large group of cells (18/44; 41%) decreased their activity exclusively in the IG task, and only three of the cells (7%) decreased their activity exclusively in the VT task. Although the numbers were not large, this pattern was similar across the four nuclei examined.

Cells that were active exclusively at the end of the movement constituted only 9% (18/203) of our sample. A much larger proportion of cells (84/203; 41%) displayed increases in activity during the movement that remained above baseline

levels after the end of the movement (see for example, the cell depicted in Fig. 2B). As mentioned in the preceding text, the activity in these cells could be related to braking the outgoing movement, initiating the return movement to the starting position, or the delivery of the reward. Unfortunately, because of the manner in which the monkey performed the experimental task, it was difficult to separate out these possibilities. We are in the process of undertaking experiments designed to address this issue and will report the results in a subsequent publication.

Thalamic stimulation

In separate sessions after all recordings had been completed, we applied microstimulation at selected sites to aid in the determination of our recording locations. Several recent studies have demonstrated that movements can be elicited at low thresholds by microstimulation within VPLo and VLc but generally not within other thalamic nuclei (Buford et al. 1996; Miall et al. 1998; Vitek et al. 1996). Thus this technique is useful in determining the location of VPLo and VLc with respect to the other nuclei.

Because this study was first and foremost a recording study, we did not complete an exhaustive series of microstimulation penetrations. Rather our goal in performing the microstimulation was to help us confirm that we had been recording from (at the very least) VPLo. Toward this end, we made 11 penetrations in one monkey and 4 in the other at sites that were presumably within one of the four nuclei examined in detail during the recordings. Consistent with the other studies cited earlier, we found that microstimulation at sites within VPLo elicited movement of the arm, hand, face, or leg at thresholds as low as 20 μ A. These sites are shown in Figs. 8 and 9 (asterisks) along with the reconstructed recording sites described in the following text. By contrast, movements could either not be evoked or required currents as high as 120 μ A to be elicited within area X, VLo, and VApc. These sites are depicted with dashes in Figs. 8 and 9. The one exception to this general finding was a low-threshold (30 μ A) microexcitable zone located at the lateral aspect of area X in the second monkey (Fig. 9D). A similar result was obtained by Buford et al. (1996) and in fact may represent microexcitable areas at the medial edge of VPLo. More importantly, however, movements were elicited at the most anterior penetrations from which we recorded that we presumed to be within VPLo. This confirmed that our VPLo recording sites were behind the interdigitated border between this nucleus and VLo.

Reconstruction of recording sites

Sagittal reconstructions of the recording sites for each monkey are shown in Figs. 8 and 9. These reconstructions were generated based on the coordinates of each recorded cell with respect to marker lesions and, when possible, the electrode tracks themselves. Each different type of symbol in Fig. 8 and 9 represents cells that displayed increases in activity in both tasks, in the VT task only, or in the IG task only. In general, there was no clear organization in which cells from the same activity category were grouped together. For example, on any single penetration we could find each type of activity category. For clarity, the reconstructed sites of cells that displayed de-

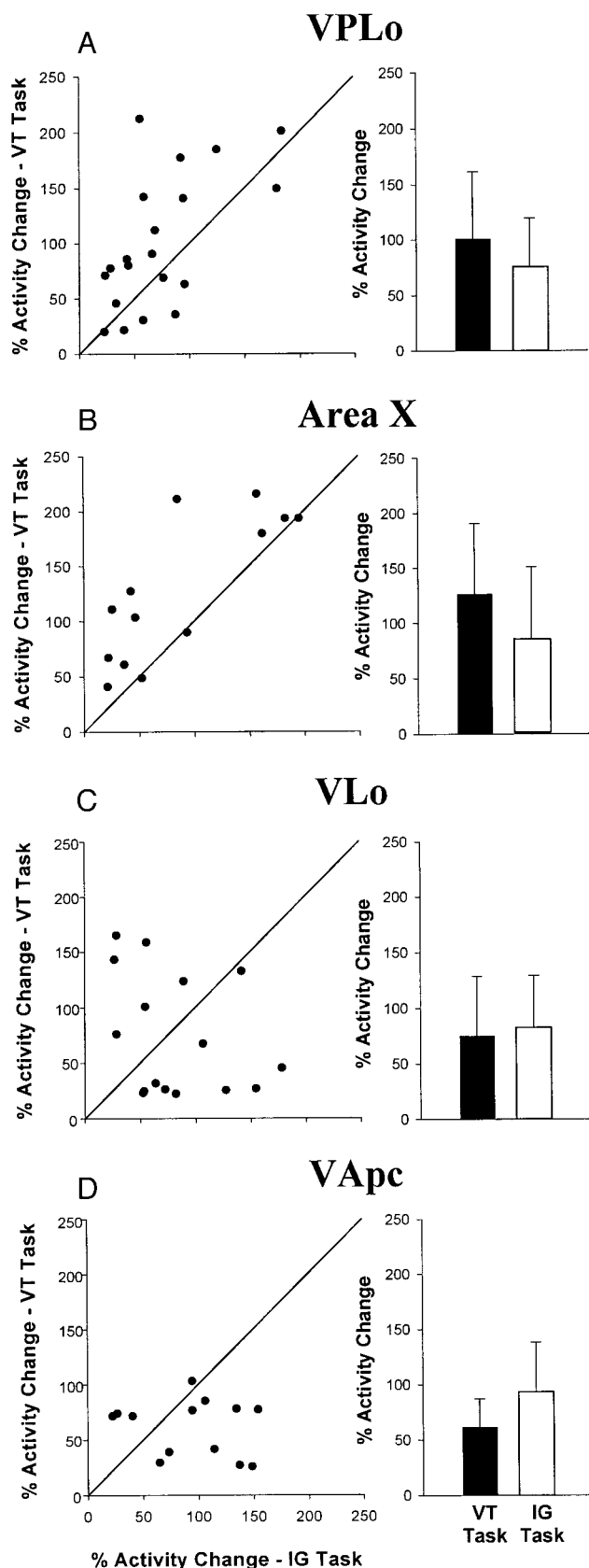


FIG. 6. *Left:* percentage change in activity in the IG task (abscissa) vs. VT task (ordinate) for cells that were active in both tasks in VPLo (A), area X (B), VLo (C), and VApc (D). Cells falling below the line of unity were categorized as displaying a preference for the IG task, whereas cells above the line of unity were categorized as preferring the VT task. *Right:* mean percentage change in activity for cells active in both the VT (■) and IG (□) tasks for each nucleus. Error bars, 1 SD.

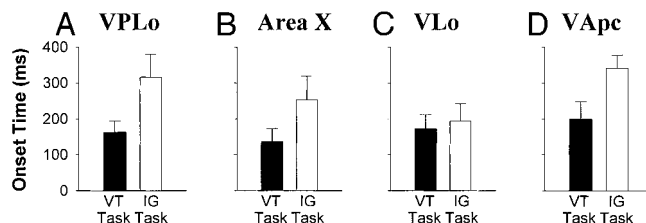


FIG. 7. Mean onset times for increases in neuronal activity in cells that fired in both the VT and IG tasks. Each bar represents the average of the onset times across the 2 monkeys. ■, data from the VT task; □, data from the IG task. Onset times for each task are shown for VPLo, area X, VLo, and VApc in A–D, respectively. Error bars, 1 SD.

creases in activity around the movement or increases at the end of movement are not shown.

DISCUSSION

Compared with the cerebellum and basal ganglia and their respective cortical projection sites, there is a relative dearth of single-unit recording studies aimed at understanding the processing occurring within the motor thalamus. One reason for this appears to be that the motor thalamus traditionally is viewed simply as a “relay” center through which subcortical structures send projections to cortical targets. Thus the same neuronal information is assumed to be present in the thalamus as in the cerebellum or basal ganglia. Although not the focus of the current study, the presence of interneurons at least within the cerebellar-receiving nuclei (Ilinsky et al. 1993) suggests that a significant amount of neuronal processing beyond a simple relay of information may be taking place within the motor thalamus. In addition, other inputs particularly those arising from corticothalamic projections also may modulate the activity of cells in the cerebellar- and basal-ganglia- receiving thalamic nuclei (see following text). These issues await further investigation.

The goal of the present study was to examine whether any functional segregation exists at the level of the thalamus in terms of the types of cues used to trigger and guide movement. In particular, we were interested in whether movements driven by external sensory stimuli as opposed to internal cues were coded differentially by different thalamic nuclei. The results demonstrated that cells in area X preferentially contributed to movements triggered by visual stimuli (VT task): just over half of the cells sampled in area X fired exclusively in the VT task, 77% of area X cells that fired in both tasks did so to a greater extent in the VT task, and as a population, the cells in area X that were active in both tasks displayed a greater depth of modulation in the VT task. By contrast, cells in VApc preferentially contributed to movements that were generated based on an internal cue (IG task): slightly more than half of the cells recorded from in VApc fired exclusively in the IG task, 69% of VApc cells active in both tasks fired to a greater extent in the IG task, and as a population, cells in VApc that fired in both tasks displayed a greater depth of modulation in the IG task. Thus the evidence clearly supports a functional distinction between area X and VApc in terms of the cues used to trigger and guide movement. In contrast to this relatively high degree of functional specificity, cells in VPLo and VLo did not show as clear a preference for one condition or the other. Approximately 1/3 of the cells in VPLo and VLo were exclusively related to the VT and IG tasks, respectively. Moreover, of the cells that were active in both tasks there was a categorical

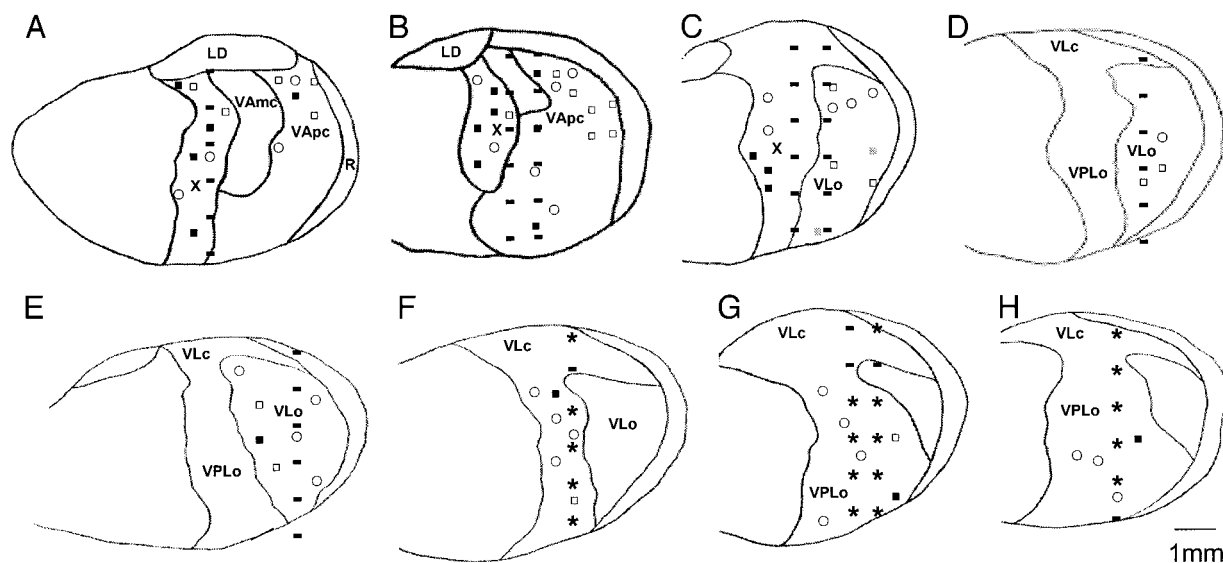


FIG. 8. Sagittal sections through the thalamus of *monkey 1* showing locations of neurons displaying increases in activity in both tasks (large white circles), increases in the VT task only (black squares), or increases in the IG task only (white squares). Asterisks denote sites from which movements of the hand, arm, leg, or face could be elicited with microstimulation. Dashes denote microstimulation sites that did not elicit movement. Sagittal slices are at 0.5-mm intervals starting at 3.5 mm lateral to the midline in *A* and ending at 7.0 mm lateral in *H*. LD, lateral dorsal nucleus; R, reticular thalamic nucleus; VAmc, ventral anterior nucleus, pars magnocellularis; VLc, ventral lateral nucleus, pars caudalis; X, area X.

tendency for more of them to be preferentially active in the VT task in VPLo and the IG task in VLo. However, as a population these cells did not display a significant difference in their depth of modulation across the two tasks. Thus although there was a slight tendency for functional specificity related to the tasks used in this study within VPLo and VLo, this tendency was much weaker than that observed in area X and VApc. Instead, most of the cells sampled in these two nuclei did not differentiate between the conditions. The present results are consistent therefore with the idea that different anatomically segregated portions of the motor thalamus are involved to varying degrees in the control of visually triggered versus internally generated movements. Preliminary evidence in which these nuclei were temporarily inactivated provides support for these conclusions (van Donkelaar et al. 1997b). In particular, only VT movements were affected after inactivation of area X, infusion of

VApc caused specific deficits in the IG task, and both tasks were influenced when either VPLo or VLo was inactivated. In what follows, we discuss how these results can be interpreted in light of previous functional and neuroanatomic studies within the cerebello- and pallidothalamocortical systems.

Cerebellum and visually triggered movements

The cerebellum is intimately involved in the generation and control of arm movements made toward visual targets. Subjects with cerebellar damage have difficulty with such movements and show improvements when vision of the target or their hand is removed (e.g., Beppu et al. 1987; van Donkelaar and Lee 1994). Brain imaging studies have demonstrated significant cerebellar activation during pointing movements made with visual feedback of the hand (Inoue et al. 1998) and when

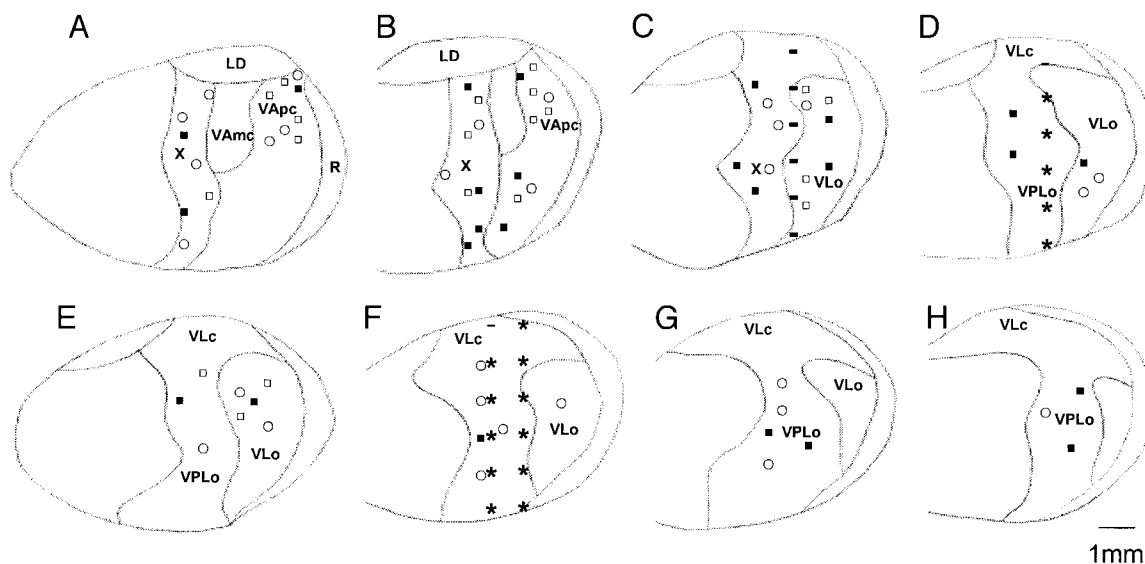


FIG. 9. Sagittal sections through the thalamus of *monkey 2*. Figure notation as in Fig. 8.

movements are triggered and guided by external sensory cues (Jueptner et al. 1996). Mushiake and Strick (1993) have shown that this functional specificity for visually guided action may be restricted at the level of the dentate to the most caudal portions of this nucleus: cells here display a preference for visually guided movements, whereas cells located more rostrally in the dentate do not differentiate as clearly between visually guided and remembered movements. The caudal dentate projects mainly to area X whereas the rostral dentate projects mainly to VPLo (Strick et al. 1993). Thus there is a clear association between the functional specificity observed at the level of the dentate as shown by Mushiake and Strick (1993) and the functional specificity in area X and VPLo within the thalamus in the present study.

Basal ganglia and internally generated movements

Evidence to support the idea that the basal ganglia are involved preferentially in internally generated movements is less clear than that supporting the role of the cerebellum in visually triggered movements. Certainly, subjects with Parkinson's disease display deficits in producing internally generated or remembered movements that are ameliorated when external cues are provided (e.g., Crawford et al. 1989; Morris et al. 1996; Oliveira et al. 1997). Similarly, subjects with Huntington's disease have difficulty generating predictive saccadic eye movements (Tian et al. 1991). Many recording and inactivation studies in monkeys, however, have shown that the basal ganglia do not clearly differentiate between visually triggered and internally generated or remembered movements (e.g., Hikosaka and Wurtz 1983a,b; Inase et al. 1996a; Kimura et al. 1992; Mink and Thach 1991a,b). The results of Mink and Thach (1991a,b) and Inase and coworkers (1996a) are consistent instead with the idea that the basal ganglia are involved in turning off or biasing muscle activity to allow a particular movement to occur regardless of the context. On the other hand, others have demonstrated that the activity in basal ganglia output cells provides an internal cue that contributes to the switching from one movement to another within a predictable sequence (Brotchie et al. 1991). Indeed, Mushiake and Strick (1995) have shown that this functional specificity may be localized to specific portions of the internal segment of the globus pallidus (GPi). In particular, they showed that the majority (65%) of cells located in the dorsal part of the GPi fire preferentially during remembered movements, whereas the majority of cells located more ventrally in the GPi did not differentiate between visually triggered and remembered movements. The key issue with respect to these discrepant results appears to be the location at which the recording or inactivation took place within the GPi. In the experiments by Mink and Thach (1991a,b) and Inase and colleagues (1996a) the mid to ventral half of the GPi was probed, whereas in the Mushiake and Strick (1995) study, a distinction between the dorsal and ventral parts of the GPi was made. Taken together, these results imply that the basal ganglia are involved in general in the process of movement selection or inhibition regardless of the context (Mink 1996), but that the dorsal aspect of the GPi is involved more specifically in the process of movement selection based on internal cues.

The dorsal GPi projects mainly to the lateral and rostral aspects of VLo and VApc, whereas the ventral GPi projects to

the middle portion of VLo (DeVito and Anderson 1982). Unlike the relatively segregated projections from the cerebellum to VPLo and area X, there appears to be a substantial amount of overlap in the pallidal projections to VLo and VApc (DeVito and Anderson 1982). Thus it is not clear how the results of the present study on the ventral thalamus and those by Mushiake and Strick (1995) on the GPi are to be integrated. The fact that cells in VApc displayed a strong preference for internally generated movements but cells in VLo did not despite receiving inputs from the dorsal GPi suggests that other inputs may be modulating the activity in the motor thalamus in a task-specific fashion. One such input may be that arising from motor cortical projections back down to the thalamus. Therefore the interactions between the thalamus and the motor areas of the cortex will be considered next.

Thalamocortical and corticothalamic projections

The projections from the cerebellar- and pallidal-receiving portions of the thalamus overlap considerably at the level of the cortex (e.g., Holsapple et al. 1991; Hoover and Strick 1993, 1999; Inase and Tanji 1995; Inase et al. 1996b; Matelli and Luppino 1996). For example, VPLo sends projections to the motor cortex, the dorsal and ventral premotor cortex, and the supplementary motor area. VLo also sends projections to each of these areas as well as to the presupplementary motor area. In terms of function, the finding from the present study implies that the majority of cells in VPLo and VLo contribute similar signals to each of these areas during movements based on external visual cues versus internal cues.

The projections from both area X and VApc terminate in the ventral premotor cortex, the presupplementary motor area, and the frontal and supplementary eye fields. The degree to which area X and VApc projections overlap categorically at the cortical level is difficult to reconcile with our results showing functional segregation between these nuclei in terms of the cues used to trigger and guide movement. When the strength of the projection is taken into account, however, the relationship between activity in area X and VApc and their cortical projection sites becomes somewhat more tractable. Area X projects more heavily to the ventral premotor cortex than does VApc (Matelli and Luppino 1996; Matelli et al. 1989). The ventral premotor cortex has been shown to integrate oculomotor and hand movement signals during responses triggered and guided by external sensory cues (Fujii et al. 1998; Mushiake et al. 1997). In addition, the number of cells in the ventral premotor cortex that are related to visually triggered movements is two to three times greater than the number of cells related to internally guided movements (Mushiake et al. 1991). This is very similar to our own finding that the activity in the majority of cells in area X is related to visually triggered movements.

Relative to area X, VApc sends a somewhat stronger projection to the presupplementary motor area (Matelli and Luppino 1996). Brain-imaging studies have demonstrated that this area participates in the selection of motor responses based on memorized information (Petit et al. 1998; Picard and Strick 1996) but does not contribute to visually triggered pointing movements (Inoue et al. 1998). The results from recording and inactivation studies in primates are consistent with these findings. Cells in the presupplementary motor area participate in the acquisition and control of memorized sequences of move-

ments (Clower and Alexander 1998; Nakamura et al. 1998). Similarly, temporary inactivation of the presupplementary motor area disrupts the ability to produce memorized but not visually triggered sequences of movements (Shima and Tanji 1998). These results are similar to our own showing a preference for movements based on internal cues within VApC.

The projections from the motor thalamus to the motor areas of the cortex are to a certain extent reciprocal. Both the motor cortex and supplementary motor area project to VPLo and VLo but not area X or VApC (Jurgens 1984; Kunzle 1976). By contrast, the ventral premotor cortex and the anterior portion of the supplementary motor area (i.e., the presupplementary motor area) project to area X and VApC but not VPLo or VLo (Kunzle 1978). The projection from the motor cortex to VPLo and VLo could help to explain the lack of clear task specificity observed in these nuclei in the present study. The motor cortex codes for the basic parameters of movement like force and direction (Georgopoulos 1991) and does not differentiate between movements based on external cues versus internal cues (Mushiake et al. 1991). If the input from the motor cortex modulates or even dominates the activity in VPLo and VLo, then it follows that they too will not differentiate between the tasks used in the present study.

Conclusions

The present experiment was designed to test whether the neuronal processing in the cerebellar- and basal-ganglia-receiving nuclei of the motor thalamus was consistent with the functional specificity previously suggested for these subcortical structures during visually triggered and internally generated limb movements. We have demonstrated that cells located in area X showed a strong preference for visually triggered movements; whereas cells located in VApC displayed a strong preference for internally generated movements. In each case, more than half of the cells recorded in these areas coded exclusively for their preferred movement condition. By contrast, cells located in VPLo and VLo did not as clearly differentiate between the two movement tasks. Taken together, these results are consistent with the hypothesis that specific subcircuits within the cerebello-thalamo-cortical and basal ganglio-thalamo-cortical pathways clearly differentiate between visually triggered and internally generated movements, respectively.

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